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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,091	07/15/2003	Steve Roffler	4910-2DIV2	8710

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,091	ROFFLER ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 21-37 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 21-37 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 21-37 are currently pending and under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 07/15/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

The disclosure is objected to because of the following informalities: The specification on page 1 should be amended to reflect the priority status of the present application, for example:

This application is a divisional of U.S. Patent Application Serial No. 09/810,379, filed on March 16, 2001 now U.S. Patent Number 6,617,118, which is a divisional of U.S. Patent Application Serial No. 09/520,225, filed on March 7, 2000 now U.S. Patent Number 6,596,849, which claimed priority from U.S. Provisional Patent Application Serial No. 60/136,522, filed on May 28, 1999, each of which is incorporated by reference.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-32 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "means" used in describing tumor targeting and for activating an anti-tumor prodrug recited in claim 29 is a relative term which renders the claim indefinite. The term "means" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the instant case, it is unclear whether the term "means" refers to a method by which a tumor is targeted or a method by which a anti-tumor prodrug is activated or whether the term "means" refers to an actual agent, such as an antibody for the tumor targeting or an enzyme for the activation of a prodrug.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of polyethylene glycol-containing compounds, which are cleared by an anti-polyethylene glycol antibody, and a genus of polyethylene glycol-containing conjugates comprising a tumor targeting means and a means for activating a genus of anti-tumor prodrug used for treating a tumor. However, the written description in this case only sets forth a polyethylene glycol-containing compound consisting of a PEG-modified βG which may be further

covalently linked to a $F(ab')_2$ fragment of mAb B72.3 or mAb H25 and one species of polyethylene glycol-conjugates used for the treatment of a tumor, wherein the tumor targeting "agent" is a $F(ab')_2$ fragment of mAb B72.3 covalently linked to a PEG-modified βG which activates one species of prodrug referred to as the tetra n-butyl ammonium salt of glucuranoid derivative of p-hydroxyaniline mustard.

The specification teaches (page 8, lines 11-13) that specific polyethylene glycol-containing compounds of the invention include, but are not limited to, compounds which are cleared from the circulation by an antibody against PEG with out significant toxic side effects. The specification further teaches (page 8, lines 9-11 and page 9, lines 7-9) the development of PEG-modified compounds which are useful in cancer therapy, wherein the PEG-containing compound comprises a tumor targeting means and a means for activating an anti-tumor prodrug to the patient. Although the specification (page 19) discloses the accelerated clearance of two polyethylene glycol containing compounds comprising a PEG-modified βG covalently linked to mAb's B72.3 or H25, the written description (page 43, lines 3+) only appears to reasonably convey one species polyethylene glycol-conjugates used for the treatment of a tumor, wherein the tumor targeting "agent" is a $F(ab')_2$ fragment of mAb B72.3 covalently linked to a PEG-modified βG which activates one species of prodrug referred to as the tetra n-butyl ammonium salt of a glucuranoid derivative of p-hydroxyaniline mustard. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of compounds that encompass the genus of polyethylene

glycol-containing compound which are rapidly cleared from blood circulation by administration of an anti-polyethylene glycol antibody nor does it provide a description of structural features that are common to the compounds. Further, the specification fails to provide a representative number of conjugates that encompass the genus of polyethylene glycol-containing conjugates comprising a tumor targeting means and a means for activating a genus of anti-tumor prodrug used for treating a tumor nor does it provide a description of structural features that are common to the conjugates. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of two species of polyethylene glycol-containing compounds, which are cleared by an anti-polyethylene glycol antibody and one species of polyethylene glycol-containing conjugates comprising one tumor targeting means and one means for activating a single anti-tumor prodrug used for treating a tumor is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of polyethylene-gylcol containing compounds and conjugates, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only two species of polyethylene glycol-containing compound consisting of a PEG-modified βG which may be further covalently linked to a $F(ab')_2$ fragment of mAb B72.3 or

mAb H25 and one species of polyethylene glycol-conjugates used for the treatment of a tumor, wherein the tumor targeting "agent" is a $F(ab')_2$ fragment of mAb B72.3 covalently linked to a PEG-modified βG which activates one species of prodrug referred to as the tetra n-butyl ammonium salt of glucuranoid derivative of p-hydroxyaniline mustard, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 21-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng et al. (Bioconjugate Chem. 1999; 10: 520-528, IDS).

Cheng et al. disclose a method of accelerating the clearance of polyethylene glycol-modified proteins by the administration of anti-polyethylene glycol IgM (entire document). With regards to the administration, the reference teaches the anti-polyethylene glycol antibody may be administered 24 hours after the administration of the polyethylene glycol conjugate (page 524, 1st column 1st paragraph). With regards to the polyethylene glycol-modified protein, Cheng et al. teach that the polyethylene glycol modified protein comprises β-glucuronidase (abstract). With regards to the anti-polyethylene glycol antibody, the reference teaches that the anti-polyethylene glycol antibodies are monoclonal antibodies and further comprise the addition of galactose so as to be targeted by asialoglycoprotein receptor on a hepatocyte (page 521, 1st column, 1st paragraph bridging page 520).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (Cancer Imunol. Immunother. 1997; 44: 305-315, IDS) in combination with Cheng et al. (Bioconjugate Chem. 1999; 10: 520-528, IDS).

Cheng et al. (1997) teaches poly(ethylene glycol) modification of β-glucuronidase-antibody conjugates for solid-tumor therapy by targeted activation of glucuronide prodrugs. Specifically, the reference teaches a method of treating a tumor in a patient, wherein the method comprises: a) administering a polyethylene glycol-containing conjugate consisting of an antibody that binds to the surface of AS-30D hepatoma cells covalently linked to a β-glucuronidase; and b) administering the glucuronide prodrug of p-hydroxyaniline mustard (abstract) 4 to 5 days after the administration of the conjugate.

Cheng et al. (1997) does not teach the administration of an anti-polyethylene glycol antibody to accelerate the clearance of the polyethylene glycol-containing compound. Nor do Cheng et al. (1997) teach any of the characteristics of the anti-polyethylene glycol antibody.

Cheng et al. (1999) disclose a method of accelerating the clearance of a polyethylene glycol-modified proteins consisting of a PEG modified β-glucuronidase by the administration of anti-polyethylene glycol IgM (entire document). With regards to the administration, the reference teaches the anti-polyethylene glycol antibody may be administered 24 hours after the administration of the polyethylene glycol conjugate (page 524, 1st column 1st paragraph). With regards to the anti-polyethylene glycol antibody, the reference teaches that the anti-polyethylene glycol antibodies are monoclonal antibodies, wherein the antibodies may be further derivatized with galactose so as to be targeted by an asialoglycoprotein receptor on a hepatocyte (page 521, 1st column, 1st paragraph bridging page 520).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer an anti-polyethylene glycol antibody as a clearing agent in the method of treating a tumor as taught by Cheng et al. (1997) in view of the teachings of Cheng et al. (1999). One would have been motivated to do so because as taught by Cheng et al. (1999), accelerated clearance of conjugates from the circulation may allow for earlier prodrug administration

when the greatest amount of conjugate is present at tumor cells (page 521, 1st column, 1st paragraph bridging page 520). Thus, one of skill in the art would have a reasonable expectation of success that by administering an anti-polyethylene glycol antibody in view of Cheng et al. (1999) prior to the administration of the prodrug as taught by Cheng et al. (1997), one would achieve a method of a tumor in a patient which requires less time between the administration of the conjugate and prodrug.

Claims 21-25, 28-33 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (US Patent 6,077,499, 2000) in combination with Richter et al. (Int. Archs Allergy Appl. Immun. 1983: 70; 124-131) in further view of Hershfield et al. (Proc. Natl. Acad. Sci. 1991; 88: 7185-7189).

Griffiths et al. teaches a method of treating a tumor comprising administering a first conjugate, which contains a tumor targeting moiety, a therapeutic agent, and a fist member of a binding pair; than administering a clearing agent to clear non-tumor targeted first conjugates; and than administration of a second conjugate which contains the complementary binding member of the binding pair and a second therapeutic agent (column 2, lines 20-27). With regards to the therapeutic agent, the patent teaches (column 9, lines 1-23) that a therapeutic agent includes, but is not limited to, a prodrug such as p-hydroxyaniline mustard, wherein the first conjugate comprises beta-glucuronidase and the second conjugate includes the prodrug which binds to the enzyme and is converted to the active metabolite. Griffiths et al. further disclose that the therapeutic agents can be a PEG derivative (column 12, lines 53-60). With regards to the clearing agent, the patent teaches (column 10, lines 23-57) that the clearing agent is a monoclonal antibody, wherein the antibody may contain multiple galactose substitutions which ensures the rapid clearance of the MAb into the liver of hepatocytes.

Griffiths et al. does not teach that the antiboy used in the clearance step is an anti-polyethylene glycol antibody. Nor does Griffiths teach that the timing in which the anti-polyethylene glycol antibody was administered after administration of the polyethylene glycol conjugate.

Richter et al. teach a polyclonal antibody which has specificity to the CH2CH2 moiety of polytheylene glycol (page 130, 1st column).

Hershfield et al. teaches the administration of wild-type PEG-PNP in mice, wherein the mice developed significant level of antibodies which correlated with marked decline in the amount of PNP circulating.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer to a patient a anti-polyethylene glycol antibody as taught by Richter et al. as a clearing agent in the method taught by Griffiths et al.. One would have been motivated to do so because as taught by Hershfield et al., antibodies developed against a PEG containing protein accelerates the clearance of the protein conjugate as evidenced by a marked decline in the amount of protein in circulation. Thus, one of ordinary skill in the art would have a reasonable expectation of success that the administration of an anti-polyethylene glycol antibody prior to the administration of the prodrug would result in the effective clearance of any non-tumor targeted first conjugates.

Furthermore, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the administration times of the clearing agent, i.e. anti-polyethylene glycol antibodies. One would have been motivated to do so because as taught by Griffiths et al, a sufficient amount of time has to occur before the administration of the clearing agent such that the first conjugate has enough time to localize to the tumor site. Therefore, the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results, see In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) or In re Gibson, 39 F.2d 975. Thus, one would have a reasonable expectation that the administration of an anti-polyethylene glycol antibody less than 5 days, 24 hours to 5 days or less than 10 days after the administration of the first conjugate would achieve a successful method of treating a tumor.

Claims 21-26, 28-34 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (US Patent 6,077,499, 2000) in combination with Richter et al. (Int. Archs Allergy Appl. Immun. 1983: 70; 124-131) and Hershfield et al. (Proc. Natl. Acad. Sci. 1991; 88: 7185-7189) in further view of Springer (US 4,427,653, 1984).

Neither Griffiths et al., Richter et al. or Hershfield et al teach that the anti-polyethylene antibody is a monoclonal antibody.

However, methods of making monoclonal antibodies are well known in the art as evidenced by the teachings of Springer (entire document). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to generate monoclonal antibodies to PEG. One would have been motivated to do so because as taught by Griffiths, the preferred clearing agent is a monoclonal antibody (column 10, lines 29-35). Thus, one would have a reasonable expectation that the administration of a monoclonal anti-polyethylene glycol antibody prior to the administration of the prodrug would result in the effective clearance of any non-tumor targeted first conjugates.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
8/24/05